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INTERSTITIAL CYSTITIS: CURRENT ISSUES AND CONTROVERSIES IN DIAGNOSIS

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ABSTRACT

Current tests for the diagnosis of interstitial cystitis (IC) are reviewed, including clinical assessment, urodynamic testing, cystoscopy, bladder biopsy, and urinary markers. A MEDLINE search was performed of all studies dealing with the diagnosis of IC. These studies were critically reviewed with the goal of arriving at a utilitarian approach to IC diagnosis. IC is being diagnosed with increasing frequency. However, the diagnostic criteria are nonuniform and there is significant overlap between chronic pelvic pain syndromes in men and women and IC. Diagnosis of IC can be made clinically and by cystoscopy and hydrodistention. The sensitivity and specificity of urinary markers have not been prospectively studied. Individual practitioners continue to use the various diagnostic tests. There is a clear need for uniform diagnostic criteria for clinical diagnosis as well as epidemiologic and research studies. UROLOGY **57** (Suppl 6A): 82–88, 2001. © 2001, Elsevier Science Inc.

Interstitial cystitis (IC) is a bladder syndrome characterized by pelvic pain and irritative voiding symptoms.[1] As originally described, diagnosis required the cystoscopic findings of Hunner's ulcers and a severely reduced bladder capacity. This definition of "classic" or ulcerative IC remained the gold standard until Messing and Stamey[2] described the more common type of "nonulcer" IC characterized by glomerulations and submucosal hemorrhages after cystoscopy and hydrodistention under anesthesia.

In the mid 1980s, the increasing prevalence of IC and the emergence of the Interstitial Cystitis Association (ICA) as a patient advocacy group led the National Institutes of Health–National Institute of Diabetes and Digestive and Kidney Diseases (NIH-NIDDK) in the United States of America to promulgate clinical and cystoscopic diagnostic criteria for *research studies* of IC.[3] These criteria, which include clinical exclusions and the cystoscopic findings of ulcers and glomerulations, were then widely adopted for clinical and drug studies. Regrettably, the NIH-NIDDK criteria for research studies inadvertently became the defacto criteria for clinical diagnosis.[4]

Limitations of the NIH-NIDDK criteria as they relate to clinical practice soon surfaced. For example, IC occurs in children and adolescents[5] notwithstanding the fact that the NIH criteria require that patients be >18 years of age. The NIH IC Database (ICDB) Study revealed that up to 60% of patients with IC are underdiagnosed if diagnosis is based on the strict NIH-NIDDK criteria.[4] These limitations raised the possibility that IC could be diagnosed clinically without recourse to cystoscopy and hydrodistention. The intravesical potassium sensitivity test[6] and urinary markers[7,8] such as glycoprotein-51 (GP-51) and antiproliferative factor (APF) have been suggested as a diagnostic tests for IC. Each of these approaches has proponents and detractors and currently there is no universally accepted technique for diagnosis of IC.

IC patients frequently have overlapping symptoms related to the pelvic organs—urologic, gastrointestinal, gynecologic, and pelvic floor including the prostate.[9] It may well be that patients with other pain and frequency syndromes such as the frequency–urgency syndrome, painful bladder syndrome, chronic pelvic pain syndrome, etc. (Table I) actually have IC. Some IC patients have a preponderance of pain symptoms with minor or absent symptoms of frequency and urgency, others have bladder symptoms and no pain and yet others

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have both pain and bladder irritability. The recognition that women with chronic pelvic pain (CPP) and men with nonbacterial prostatitis and prostatodynia (CPP syndrome) may have IC[10,11] has highlighted the need for an expanded, multispecialty definition of IC.

This article reviews the current diagnostic tests for IC with particular regard to their limitations and advantages. The need for a new, broader diagnostic paradigm is emphasized and a plea is made for uniform, worldwide diagnostic criteria for clinical, epidemiologic and research studies.

CURRENT APPROACH TO DIAGNOSIS

National Institutes of Health–National Institute of Diabetes and Digestive and Kidney Diseases Clinical and Cystoscopic Criteria

The promulgation of the NIH-NIDDK criteria for the *research* diagnosis of IC led to increasing numbers of patients being diagnosed (Table II). An inadvertent drawback is the fact that clinicians adopted the research criteria for everyday clinical practice. In effect, the NIH criteria became the defacto criteria for clinical diagnosis.

The utility of these strict research criteria was evaluated in the ICDB Study which concluded that the NIH-NIDDK criteria were too restrictive for clinical use.[4] More than 60% of patients regarded by experienced clinicians as having IC fail to meet the NIH-NIDDK criteria. Conversely, 90% of patients who meet the NIH criteria for diagnosis were believed by the clinicians to have IC. The ICDB concluded that the restrictive NIH-NIDDK criteria, although excellent for research studies, were not suitable for routine clinical use.

Based on the ICDB findings, clinicians are increasingly comfortable diagnosing IC on the basis of symptoms (frequency, urgency, nocturia, and pain) in the absence of known infectious and/or neoplastic diseases. Routine urine culture and cytology can exclude the latter. Patients with significant microscopic hematuria require cystoscopy to exclude neoplastic lesions of the bladder.[12] Physical examination frequently reveals anterior vaginal wall and bladder base tenderness in women. This purely clinical approach to diagnosis is particularly appealing to patients who want to avoid the risks, morbidity and discomfort of cystoscopy and hydrodistention under anesthesia.

Individual patients request, and certain urologists continue to recommend cystoscopic evaluation under anesthesia as part of the work-up. The pluses of this approach include photodocumentation of the bladder inflammation (glomerulations, submucosal hemorrhages, ulcers), determination of the bladder capacity under anesthesia and delineation of the degree and type of microscopic inflammation, if biopsies are performed.[13] Additionally, hydrodistention is therapeutic in 20% to 30% of patients who get relief for 3 to 6 months after distension.[1]

The cystoscopic and biopsy findings can be useful in counseling on treatment and prognosis.[13] Individuals with severely reduced bladder capacity and ulcers respond less favorably. With advances in understanding pathophysiology and pathogenesis, it is probable that biopsy data will identify IC subgroups with differing therapeutic potentials (eg, patients with mastocytosis that can be treated with antihistamines). Patients with markedly reduced bladder capacities and scar tissue on biopsy are less likely to respond to pharmacologic treatment and more likely to need surgical treatment.

It has long been recognized that glomerulations are not pathognomonic of IC and they can be seen

TABLE I. ***Interstitial cystitis: overlapping syndromes***

- Interstitial cystitis
- Painful bladder syndrome
- Frequency-urgency syndrome
- Pelvic pain syndromes
- Overactive bladder syndrome

TABLE II. ***Current diagnosis of interstitial cystitis (IC)***

- Clinical
  - —Pain, bladder irritability
  - —Exclusion infection/cancer
  - —Symptom scores (eg, O'Leary-Sant)
- Clinical and cystoscopic (NIH-NIDDK)
  - —Ulcer, nonulcer IC
  - —General, spinal anesthesia
  - —60% rate of underdiagnosis
  - —useful in prognosis
- Bladder biopsy
  - —Country/region specific
  - —Low diagnosis rate
  - —Morbidity
  - —Treatment predictors
- Urodynamics
  - —No need for complex UDS
  - —Sensory instability
  - —Motor instability
- Potassium sensitivity test
  - —25% rate of underdiagnosis
  - —False-positive/false-negative
  - —Potentially painful
- Urinary markers
  - —GP-51, APF
  - —Potentially useful

APF = antiproliferative factor; GP-51 = glycoprotein-51; IC = interstitial cystitis; NIDDK = National Institute of Diabetes and Digestive and Kidney Diseases; NIH = National Institutes of Health; UDS = urodynamics.

in defunctionalized bladders and after intravesical chemotherapy.[1,14,15] This lack of specificity of glomerulations was highlighted in a recent study that reported the presence of glomerulations in up to 40% of "normal" women undergoing tubal ligation.[16] In this study, the women were not specifically questioned about urinary symptoms, carefully assessed for gynecologic symptoms of chronic pelvic pain or asked to complete voiding logs or pain scores. It is possible, therefore, that some of these women may have had early or mild IC characterized by pelvic pain and/or irritative voiding symptoms.

Some of the NIH-NIDDK exclusion criteria have proven problematic in clinical practice. The age exclusion criterion (<18 years) is clearly untenable as IC occurs in children and adolescents.[5,17] Although involuntary bladder contractions on urodynamics is an NIH-NIDDK exclusion criterion, the ICDB reported involuntary bladder contractions in 14.6% of IC patients.[18] As noted earlier, the major symptom in some IC patients is pain (bladder, pelvic) with minimal or absent irritative voiding symptoms (frequency, nocturia). Clearly, this subgroup of patients does not satisfy the NIH-NIDDK criteria.

Intravesical Potassium Sensitivity Test: Parson's Test

The intravesical potassium sensitivity test was introduced by Parsons in 1994[19] and later assessed in a large group of patients. Overall, 75% of patients with IC (equal numbers of patients satisfying the NIH-NIDDK research criteria and clinical criteria without cystoscopy) had positive potassium sensitivity tests.[6] In this test, a dilute solution of potassium (40 mEq in 100 mL of water) is left in the bladder for 5 minutes. The patient then rates the degree of provocation with urgency and frequency on a scale of 0 (no provocation) to 5 (marked provocation). A positive test is defined by a change in score of ≥2. The potassium sensitivity test has been advocated as a minimally invasive, office diagnostic test for IC.

However, as the test is positive in only 75% of patients, at least one quarter (25%) of patients with IC (with either clinical or NIH research criteria) will remain undiagnosed. The test is also positive in patients with detrusor instability (25%), radiation cystitis (100%), and bacterial cystitis (100%). False negative tests occur with severe disease and after treatment.[6,19]

The utility of the potassium sensitivity test for diagnosis of IC was assessed in a single institution study from Canada involving 39 patients with suspected IC.[20] The test was positive in 66% whereas the cystoscopy and hydrodistention was positive in 59%. With a sensitivity of 69.5% and a specificity of 59%, the investigators concluded that the intravesical potassium sensitivity test was not a valid diagnostic tool. They recommended that IC should be diagnosed on the basis of clinical symptoms and endoscopic findings (ie, NIH-NIDDK criteria).

The potassium sensitivity test is based on the hypothesis of increased epithelial permeability in IC, which results in diffusion of potassium into the submucosal and detrusor layers of the bladder resulting in nerve depolarization, chronic inflammation, and injury.[6,19] An alternative explanation may be primary neurogenic inflammation. The fact that 25% of patients with detrusor instability have positive tests favors a neurogenic mechanism because the etiology of detrusor instability is both neurogenic and myogenic.

The potassium sensitivity test may well identify a subgroup of IC patients with epithelial permeability dysfunction. This may allow targeted therapeutic intervention with drugs such as sodium pentosan polysulfate that reverse epithelial dysfunction. A recent study suggested that the potassium sensitivity test is predictive of response to sodium pentosan polysulfate.[21] However, a drawback to this study was that many patients also received amitriptyline HCl, which is known to be effective in neurogenic inflammatory conditions.[22]

Further studies are needed to clarify the role of the potassium sensitivity test in IC diagnosis, and to resolve the divergent viewpoints on the pathogenetic mechanism underlying the test.

Urodynamic Testing

Although many dispute the need for urodynamic evaluation, it may be useful to exclude detrusor instability as a cause of irritative voiding symptoms. There is significant overlap between the symptoms of the overactive bladder syndrome and those of IC (ie, frequency, urgency, and urge incontinence). On simple urodynamics, many IC patients have sensory urgency and instability, reduced bladder capacities, and pain with bladder filling at low volumes.[23,24]

The ICDB study demonstrated positive correlations between symptoms of frequency and maximal cystometric capacity and bladder volume at the first sensation to void. There was no urodynamic correlation between the cystometric findings and body pain and global health. Interestingly, 14.6% (56 of 384 patients) had uninhibited detrusor contractions.[18]

The current consensus is that urodynamics is not required for diagnosis of IC, but may provide useful information on the differential diagnosis of painful voiding disorders and the symptoms of the overactive bladder.[13,14] Complex video urodynamics including electromyography, urethral pressure

profilometry, etc., is not needed in the routine evaluation of patients with suspected IC.[2]

A modified urodynamic test including an epithelial leak test, a cystometrogram (CMG), and repeat CMG after bladder emptying and instillation of intravesical lidocaine may discriminate between bladder and nonbladder symptoms of IC.[25] However, this technique has not been prospectively evaluated or compared with the "gold standard" of cystoscopy and hydrodistention.

Bladder Biopsy

The role of bladder biopsy in the diagnosis of IC is unclear. Most North American urologists make the diagnosis of IC on clinical or clinical plus cystoscopic criteria without the need for bladder biopsy. Bladder biopsy may be useful to stratify patients with specific pathogenetic pathways[13] and to exclude specific bladder diseases (eg, carcinoma-in–situ).[12] However, biopsy is not essential for diagnosis. It may help in counseling patients on their prognosis it terms of the degree and type of inflammatory changes, degree of fibrosis, etc.

Interestingly, bladder biopsy is regarded as essential for diagnosis in many studies reported from Europe and elsewhere.[24,26,27] This reliance on biopsy criteria for diagnosis may explain the lower reported incidence of IC in Europe and Japan compared with North America. There are no specific pathognomonic features for the diagnosis of IC and IC is most likely a heterogeneous syndrome with multiple etiologies. At best, pathologic criteria may prove specific for individual etiologies and not pathognomonic for all cases of IC. Although light microscopy can differentiate ulcerative from nonulcerative IC, the findings are insufficient to discriminate IC from other bladder pathologies.[28]

Urinary Markers

The search for noninvasive techniques for the diagnosis of IC has led to the assessment of a variety of urinary markers. A subgroup of IC patients has increased numbers and activation of mast cells[29,30] and this is paralleled by increased levels of urinary histamine, histamine metabolites, such as methylhistamine, and tryptase, a specific mast cell enzyme.[31] Other urinary markers that have been suggested as markers for the diagnosis of IC include urinary nitric oxide, glycosaminoglycans, epinephrine, nitric oxide syntase, cyclic guanosine monophosphate and interleukin-1B.[32] However, as with the mast cell metabolites, none of these markers have been prospectively studied as a diagnostic tool for IC.

Recently, a urinary APF has been described in IC and levels of this marker are increased in IC patients.[7] The urinary GP-51 may also be a clinical marker of IC.[8] However, neither of these markers has been assessed prospectively for diagnosis of IC. Ongoing studies are attempting to correlate urinary levels of GP-51 and APF with cystoscopic and biopsy findings as well as treatment outcomes.

TABLE III. *Underdiagnosed and misdiagnosed interstitial cystitis*

Chronic pelvic pain syndromes
• Women
• Men
—Nonbacterial prostatitis
—Prostatodynia
"Overactive" bladder syndrome
• Frequency
• Urgency
• Unresponsive to anticholinergics
Recurrent "cystitis" in women
• Pyuria positive
• Culture negative
• Unresponsive to antibiotics

RESERVOIR OF UNDERDIAGNOSED AND MISDIAGNOSED INTERSTITIAL CYSTITIS

The undue reliance on the cystoscopic criteria (NIH-NIDDK criteria) for the diagnosis of IC has led to significant underdiagnosis of IC, as demonstrated in the ICDB study (Table III). IC is likely to be underdiagnosed in women with symptoms of the overactive bladder syndrome (frequency, urgency and/or urge incontinence). The diagnosis of IC needs to be considered in patients with symptoms of the overactive bladder (with and without pain) who do not respond to oral anticholinergic drugs.[13]

Many patients with IC are treated with repeated courses of oral antibiotics before they are definitively diagnosed. Urine cultures are usually negative although the patients are symptomatic and urinalysis frequently reveals pyuria.[33] IC should be considered in the differential diagnosis of patients with symptoms of cystitis who are unresponsive to antibiotics, especially when urine cultures are negative.

Up to 70% of men with symptoms of nonbacterial prostatitis and prostatodynia have the cystoscopic appearance (NIH-NIDDK criteria) of IC when cystoscoped under anesthesia.[34,35] This raises the possibility that IC in men frequently masquerades as nonbacterial prostatitis/prostatodynia. The recent classification of the type 3 prostatitis syndrome as chronic pelvic pain syndrome (inflammatory and noninflammatory) suggests that IC and chronic bacterial prostatitis/prostatodynia may be the same syndrome.[34,35] The symptoms in both conditions are similar, including irritative voiding symptoms, pain (pelvic, bladder,

prostate, genital), sexual dysfunction, and the comorbidities of depression and anxiety. In a pilot open-label study, sodium pentosan polysulfate (a drug used to treat IC) reduced the severity and frequency of voiding symptoms and pain, and improved the quality of life in men with the chronic pelvic pain syndrome.[36]

CPP may be the primary symptom of IC. Such patients with bladder pain, dyspareunia, and perimenstrual symptom exacerbation are frequently referred for gynecologic evaluation whereas patients with bladder irritability present to urologists and gynecologists with symptoms of the overactive bladder and are treated with oral anticholinergics. IC is a common cause of CPP in women.[11,37] A significant percentage of women with CPP remain undiagnosed after full gynecologic evaluation. Laparoscopic evaluation in this group of patients is negative or reveals microscopic endometriosis. These data strongly suggest that gynecologists, urogynecologists, and primary care physicians need to consider IC in the differential diagnosis of CPP in women.

DIAGNOSTIC PARALLELS WITH OTHER UROLOGIC CONDITIONS

The approach to the diagnosis of IC is evolving as new information about presentation, epidemiology and prevalence become available. It is clear that the previously rigid, monolithic approach to diagnosis requiring the NIH-NIDDK criteria is no longer tenable as clinicians increasingly rely on clinical diagnosis. This evolution in the diagnostic algorithm has clear parallels to the diagnosis of prostatism and benign prostatic hyperplasia (BPH).

Before the introduction of pharmacologic and minimally invasive treatments, BPH was diagnosed by cystoscopic or urodynamic techniques. Cystoscopic criteria included the presence of an enlarged prostate, and the presence of trabeculations and/or diverticula. The cystoscopic approach to diagnosis was superceded by the use of pressure/flow urodynamic studies to confirm bladder outlet obstruction. The realization that many of the symptoms associated with BPH are related to bladder overactivity led to the introduction of the term LUTS (lower urinary tract symptoms) and the development of a number of clinical symptom measures such as the AUA Symptom Score, the International Prostate Symptom Score, and quality-of-life scores. Currently, the diagnosis of BPH is usually made by symptom assessment and exclusion of prostate cancer by digital rectal examination and serum prostate-specific antigen (PSA) determination. Urodynamics and cystoscopy are reserved for patients with marked and/or atypical symptoms and those unresponsive to simple treatment.

A similar evolution is occurring with IC. As with BPH, there may be more than 1 way to make the diagnosis. For routine clinical practice, the use of a symptom score such as the O'Leary-Sant Symptom and Problem Indices,[38] and a voiding log may prove to be sufficient for diagnosis, if the urine culture and cytology are negative. At present, the O'Leary-Sant Symptom and Problem Indices are validated only for following symptom severity over time, much as the AUA Symptom Score. For epidemiologic studies, a broader symptom definition would be beneficial so as to include patients (men and women) with pelvic pain, gynecologic symptoms, and lower gastrointestinal symptoms. IC has been posited as a urogynecologic syndrome affecting all organs of the pelvic floor.[9]

INTERSTITIAL CYSTITIS DIAGNOSIS: A MILLENNIAL SYNTHESIS

Currently, there is no diagnostic tool for IC that has universal applicability. The needs of clinicians, epidemiologists, healthcare advocates and researchers are clearly different and the definition and diagnosis of IC will vary according to their particular needs. The significant worldwide variation in the approach to diagnosis and role of bladder biopsy in diagnosis are problematic.

In Europe and Japan, the reliance on histologic criteria for diagnosis may explain the reported low prevalence of the disease compared with North America. Recent studies in North America report an IC prevalence of 60 per 100,000 women.[39] This compares with prevalence estimates of 8 to 16 of 100,000 women in the Netherlands,[26] 18 of 100,000 women in Finland,[40] and only 4.5 of 100,000 women in Japan.[27] This variability in prevalence rates and the lack of uniform diagnostic criteria are major drawbacks to the study of IC.[4,13,14] The development and adoption of uniform worldwide diagnostic criteria are clearly needed.

Each approach to diagnosis has inherent limitations. The lack of prognostic information relative to bladder capacity, degree of glomerulations, ulcers, etc., hampers the purely clinical algorithm for diagnosis. The NIH-NIDDK research criteria result in the underdiagnosis of IC in 60% of patients.[4] Likewise, the intravesical potassium sensitivity test fails to diagnose IC in 25% of patients with cystoscopically confirmed (NIH criteria) or clinically suspected IC.[6,19] Urinary markers, although attractive as noninvasive diagnostic tools, remain untested. In the future, the combination of clinical symptoms, exclusion of infection and cancer, and

TABLE IV. ***Diagnosis of interstitial cystitis: future needs***

- Prospective, comparative studies
  - —NIH-NIDDK
  - —Parson's test
  - —Clinical diagnosis
  - —Urinary markers
- Separate consensus criteria for:
  - —Clinical diagnosis
  - —Research studies
  - —Population-based studies
  - —Epidemiologic studies

NIDDK = National Institute of Diabetes and Digestive and Kidney Diseases; NIH = National Institutes of Health.

elevated urinary levels of APF and GP-51 may become a simple approach to the noninvasive, noncystoscopic diagnosis of IC.

For research studies, the NIH criteria remain the gold standard as it identifies a subgroup of IC patients with specific clinical and cystoscopic findings. Bladder biopsy is best regarded as a research and potentially prognostic tool that stratifies patients with specific pathogeneses and therapeutic potential.[13,30] Finally, the role of urinary markers, such as APF and GP-51, remains to be elucidated as diagnostic tests.

There is a need for a uniform, worldwide consensus to the diagnosis of IC (Table IV). NIH needs to build on its previously recommended diagnostic criteria for research studies. The definition of IC needs to be expanded to include new and separate criteria for clinical and epidemiologic studies. The international community of urologists and gynecologists should be involved in this effort to ensure that the criteria for each category (clinical, epidemiologic, and research) achieve worldwide cachet.

REFERENCES

1. Sant GR: Interstitial cystitis. Monographs. Urology **12**: 37–63, 1991.
2. Messing EM, and Stamey TA: Interstitial cystitis: early diagnosis, pathology, and treatment. Urology **12**: 381–392, 1978.
3. Gillenwater JY, and Wein AJ: Summary of the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases Workshop on Interstitial Cystitis, National Institutes of Health, Bethesda, Maryland, August 28-29, 1987. J Urol **140**: 203–206, 1988 .
4. Hanno PM, Landis JR, Matthews-Cook Y, *et al*: The diagnosis of interstitial cystitis revisited: lessons learned from the National Institutes of Health Interstitial Cystitis Database study. J Urol **161**: 553–554, 1999.
5. Close CE, Carr MC, Burns MW, *et al*: Interstitial cystitis in children. J Urol **156**(2 Pt 2): 860–862, 1996.
6. Parsons CL, Greenberger M, Gabal L, *et al*: The role of urinary potassium in the pathogenesis and diagnosis of interstitial cystitis. J Urol **159**: 1862–1866, 1998.
7. Keay S, Warren JW, Zhang CO, *et al*: Antiproliferative activity is present in bladder but not renal pelvic urine from interstitial cystitis patients. J Urol **162**: 1487–1489, 1999.
8. Byrne DS, Sedor JF, Estojak J, *et al*: The urinary glycoprotein GP51 as a clinical marker for interstitial cystitis. J Urol **161**: 1786–1790, 1999.
9. Sant GR: Interstitial cystitis. Curr Opin Obstet Gynecol **9**: 332–336, 1997.
10. Novicki DE, Larson TR, and Swanson SK: Interstitial cystitis in men. Urology **52**: 621–624, 1998.
11. Sant GR: Interstitial cystitis in adolescent and adult women with chronic pelvic pain. Proceedings of the NIH/ICA International Research Symposium on Interstitial Cystitis, Washington, DC, October 1997 (p 32).
12. Utz DC, and Zincke H: The masquerade of bladder cancer-in-situ as interstitial cystitis. J Urol **111**: 160–161, 1974 .
13. Sant GR, and Theoharides TC: Interstitial cystitis. Curr Opin Urol **9**: 297–302, 1999.
14. Hanno PM: Diagnosis of interstitial cystitis. Urol Clin North Am **21**: 63–66, 1994.
15. Erickson DR: Glomerulations in women with urethral sphincter deficiency: report of 2 cases. J Urol **153**: 728–729, 1995.
16. Waxman JA, Sulak PJ, and Kuehl TJ: Cystoscopic findings consistent with interstitial cystitis in normal women undergoing tubal ligation. J Urol **160**: 1663–1667, 1998.
17. Farkas A, Waisman J, and Goodwin WE: Interstitial cystitis in adolescent girls. J Urol **118**: 837–839, 1977.
18. Kirkemo A, Peabody M, Diokno AC, *et al*: Associations among urodynamic findings and symptoms in women enrolled in the Interstitial Cystitis Data Base (ICDB) Study. Urology **49**(5A suppl):76–80, 1997.
19. Parsons CL, Stein PC, Bidair M, *et al*: Abnormal sensitivity to intravesical potassium in interstitial cystitis and radiation cystitis. Neurourol Urodyn **13**: 515–520, 1994.
20. Chambers GK, Fenster HN, Cripps S, *et al*: An assessment of the use of intravesical potassium in the diagnosis of interstitial cystitis. J Urol **162**: 699–701, 1999.
21. Teichman JM, and Nielsen-Omeis BJ: Potassium leak test predicts outcome in interstitial cystitis. J Urol **161**: 1791–1794, 1999.
22. Hanno PM: Amitriptyline in the treatment of interstitial cystitis. Urol Clin North Am **21**: 89–91, 1994.
23. Steinkohl WB, and Leach GE: Urodynamic findings in interstitial cystitis. Urology **34**: 399–401, 1989.
24. Toozs-Hobson P, Gleeson C, and Cardozo L: Interstitial cystitis: still an enigma after 80 years. Br J Obstet Gynaecol **103**: 621–624, 1996.
25. Teichman JM, Nielsen-Omeis BJ, and McIver BD: Modified urodynamics for interstitial cystitis. Tech Urol **3**: 65–68, 1997.
26. Bade JJ, Rijcken B, and Mensink HJ: Interstitial cystitis in the Netherlands: prevalence, diagnostic criteria and therapeutic preferences. J Urol **154**: 2035–2037, 1995.
27. Ito T, Miki M, and Yamada T: Interstitial cystitis in Japan. BJU Int **86**(6): 634–637, 2000.
28. Johansson SL, and Fall M: Clinical features and spectrum of light microscopic changes in interstitial cystitis. J Urol **143**: 1118–1124, 1990.
29. Theoharides TC, Sant GR, el-Mansoury M, *et al*: Activation of bladder mast cells in interstitial cystitis: a light and electron microscopic study. J Urol **153**: 629–636, 1995.
30. Peeker R, Enerback L, Fall M, *et al*: Recruitment, distribution and phenotypes of mast cells in interstitial cystitis. J Urol **163**: 1009–1015, 2000.
31. Theoharides TC, Pang X, Letourneau R, *et al*: Interstitial cystitis: a neuroimmunoendocrine disorder. Ann N Y Acad Sci **840**: 619–634, 1998.
32. Ehren I, Hosseini A, Lundberg JO, *et al*: Nitric oxide: a

useful gas in the detection of lower urinary tract inflammation. J Urol **162**: 327–329, 1999.

33. Warren JW, Horne LM, Hebel JR, *et al*: Pilot study of sequential oral antibiotics for the treatment of interstitial cystitis. J Urol **163**: 1685–1688, 2000.

34. Berger RE, Miller JE, Rothman I, *et al*: Bladder petechiae after cystoscopy and hydrodistension in men diagnosed with prostate pain. J Urol **159**: 83–85, 1998.

35. Sant GR, Nickel JC: Interstitial cystitis and chronic prostatitis: the same syndrome? In Nickel JC (Ed), *Textbook of Prostatitis*. Oxford, England, Isis Medical Media Ltd., 2000, pp 169–176.

36. Nickel JC, Johnston B, Downey J, *et al*: Pentosan polysulfate therapy for chronic nonbacterial prostatitis (chronic pelvic pain syndrome category IIIA): a prospective multicenter clinical trial. Urology **56**: 413–417, 2000.

37. Sant GR: Interstitial cystitis: a urogynecologic perspective. Contemp OB/GYN **43**: 119–130, 1998.

38. O'Leary MP, Sant GR, Fowler FJ, *et al*: The interstitial cystitis symptom index and problem index. Urology **49**(5A suppl):58–63, 1997.

39. Curhan GC, Speizer FE, Hunter DJ, *et al*: Epidemiology of interstitial cystitis: a population based study. J Urol **161**: 549–552, 1999.

40. Oravisto KJ: Epidemiology of interstitial cystitis. Ann Chir Gynaecol Fenn **64**: 75–77, 1975.